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ß-catenin expression in myelodysplastic syndromes and myeloproliferative neoplasms in bone marrow, in relation to CD34 and CD117 status

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ABSTRACT

Aims: The activation of the Wnt/ β-catenin signaling pathway has been demonstrated to play a crucial role in the development of myeloid neoplasms. In addition to CD34, which has been used until now in the diagnosis and staging of clonal hematopoietic diseases, myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN), CD117, which has found its place in hematopoietic diseases, also provides significant benefits in these respects. In this study, we evaluated the immunohistochemical presence and utility of β-catenin in blasts relative to other markers, as the inhibition of β-catenin activity may be an attractive therapeutic approach

Methods: By retrospectively analyzing bone marrow samples with β-catenin immune marker, we determined the staining rates, intensities, and patterns of 30 MDS, 29 MPN cases and 30 normal bone marrow controls, in comparison to the efficacy of the the well-known CD34 and CD117. We statistically interpreted the correlation between them.

Results: Based on the findings, β-catenin, which has recently been used in hematopoietic diseases and is said to have a high efficacy in acute myeloid leukemia (AML) cases, was not immunohistochemically detectable in our study. As expected, CD34 and CD117 immun markers exhibited significant blast staining. MPN cases were more prone to staining with CD117.

Conclusion: CD34 continues to be the most reliable marker for identifying blasts for diagnosing and grading bone marrow neoplasms while CD117 may have a supportive role in this process. Further investigation is required to ascertain the true effectiveness of β-catenin, a molecule that has demonstrated encouraging potential in the context of AML.

Keywords: Myelodysplastic syndrome, myeloproliferative neoplasm, β-catenin, CD34, CD117

INTRODUCTION

Both myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) are classified as clonal hematopoietic disorders. There are distinct differences between MPN and MDS, starting from the earliest presentation of the disease. Genetic damage results in the selective proliferation of hematopoietic stem cells during late myeloid differentiation.[1] Deletion of chromosome 5q [del (5q)] is one of the most frequently observed cytogenetic abnormalities in patients with de novo myelodysplastic syndromes and therapy-related MDS or acute myeloid leukemia (t-MDS/t-AML).[2] Patients with del (5q) MDS have a favorable prognosis and a low risk of transformation to AML.[3] MDS frequently evolves into acute myeloid leukemia or bone marrow failure but years are required for the development of ineffective hematopoiesis and the appearance of blast forms in bone marrow and peripheral blood; its progression is typically synonymous with the onset of acute leukemia.[4-6] It might be argued that the identification of blast count represents a crucial stage in the course of AML.

CD34 is a glycophosphoprotein cell surface antigen expressed on progenitor and early precursor bone marrow cells that is very useful in identifying the presence of 'atypical localization of immature precursors' (ALIP), a characteristic finding in MDS. With increasing maturation, CD34 expression decreases, and weak positivity or negativity is observed in the final progenitor cells.[7] An increase in the number of CD34 (+) cells and their tendency to form aggregates are indicators of acute leukemic transformation.

The c-kit protooncogene encodes a receptor tyrosine kinase that serves as a ligand for the stem cell factor. This gene is expressed in several non-hematopoietic tissues as well as malignancies.[8] C-kit receptor (CD117) was found to be expressed in multipotent hematopoietic stem cells, myeloid and/or erythroid progenitors, and B and T lymphocyte progenitors.[9] CD117 expression is at its highest level in progenitor cells at the earliest phases of hematological development, while it decreases as maturation advances.

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The highest levels of CD117 expression are observed in advanced-stage MDS and MPN cases in association with an increased percentage of blasts.[8]

The Wnt/β-catenin pathway is an signaling pathway that plays a crucial role in a variety of cell biology processes including gene expression, growth, proliferation, migration and adhesion.[10-12] Dysregulation of Wnt/β-catenin has been associated with tumorigenesis.[13-15] Researches elucidate the critical function of Wnt/β-catenin pathway activation in the development of myeloid neoplasms2. The objective of this study was to examine the immunostaining properties of β-catenin in comparison to CD34 and CD117, with the intention of identifying its potential as a reliable marker for recognizing blasts, which is essential for the diagnosis of myeloid neoplasms.

METHODS

This thesis research was authorized in 2010 by the institution of Dicle University. However, ethics committee approval was not required at that time. All procedures were carried out in accordance with the ethical rules and the principles of Helsinki Declaration of 1964, as revised in 2000.

A total of 89 bone marrow materials and bone marrow smears, including 30 samples with myelodysplastic syndrome, 29 with myeloproliferative neoplasms, and 30 normocellular bone marrow controls without any cytological atypia that never diagnosed with a hematological disorder, were examined retrospectively in accordance with the WHO criteria. Cases were eligible if they were diagnosed with MDS and MPN, regardless of subtypes and grades. The bone marrow smears were stained with Giemsa. For the immunohistochemical examination, three paraffin block cross-sections were obtained and examined with β-catenin, CD34, and CD117 immunostains.

The cases were evaluated in four categories according to the rate of staining as follows: (i) cases without bone marrow staining or with a staining rate below 5%; (ii) cases with a staining rate between 5-30%; (iii) cases with a staining rate between 31-60%; and (iv) cases with a staining rate over 61%. In the assessment based on the intensity of staining with the immunostains, cases were categorized as follows: mild-to-minimum staining as 1(+), moderate staining as 2(+) and strong staining as 3(+). The cases were categorized into four groups based on the pattern of staining: membranous, cytoplasmic, membranous/cytoplasmic, and nuclear.

Statistical Analysis

Statistical analysis were conducted with statistical package software Epi Info, version 2000 (CDC Atlanta). Chi-square test was used for the comparison of rates between the groups (with cross tabulations). In addition, ANOVA and post hoc, Tukey HSD, Kruskal-Wallis analysis of variance and t-test were used. Intergroup differences were considered statistically significant if the p-value was less than 0.05.

RESULTS

A total of 89 patients (30 MDS, 29 MPN and 30 control group) were examined in this study. Overall, 42 patients were male (47.2%) and 47 patients were female (52.8%). The mean age was 58.5 years (range, 21-79 years) for the MDS patients, 57.2 years (range, 18-79 years) for the MPN patients and 47.3 years (range, 20-82 years) for the control group. MDS patients had a significantly higher mean age compared to the patients with a normal bone marrow (p=0.03). The mean cellularity was 70.16% (35-95%) for MDS cases, 80.44% (25-75%) for MPN cases and 48.66% (25-75%) for the control group. Based on the statistical data, MPN cases demonstrated a significantly higher bone marrow cellularity (p<0.01).

Comparison of CD34 staining intensity between groups revealed a statistically significant difference (p<0.01) (**Table 1**).

Table 1. CD34 expression results in MDS, MPN and control groups

CD34 staining rates	Control Group		MDS Group		MPN Group		Total	
<%5	25	%83.3	9	%30	12	%41.4	46	%51.7
%5-30	5	%16.7	21	%70	17	%58.6	43	%48.3
>%30	0	0	0	0	0	0	0	0
CD34 staining intensity								
1(+)	5	%16.7	4	%13.3	0	0	9	%10.1
2(+)	15	%50	10	%33.3	10	%34.5	35	%39.3
3(+)	10	33.3	16	%53.3	19	%66.5	45	%50.6
CD34 staining pattern								
Cytoplasmic	29	%96.7	23	%76.7	28	%96.6	80	%89.9
Membranous /cytoplasmic	1	%3.3	7	%23.3	1	%3.4	9	%10.1
Total	**30**	**%100**	**30**	**%100**	**29**	**%100**	**89**	**%100**

MDS: Myelodysplastic Syndrome, MPN: Myeloproliferative Neoplasm

Compared to bone marrow controls, there was a high rate of CD34 staining in both MDS and MPN cases, as determined by paired comparisons (**Figure 1**). The vast majority (83.3%) of control cases exhibited a staining rate of less than 5%, whereas 70% of MDS cases and 58% of MPN cases exhibited staining rates of 5% or higher

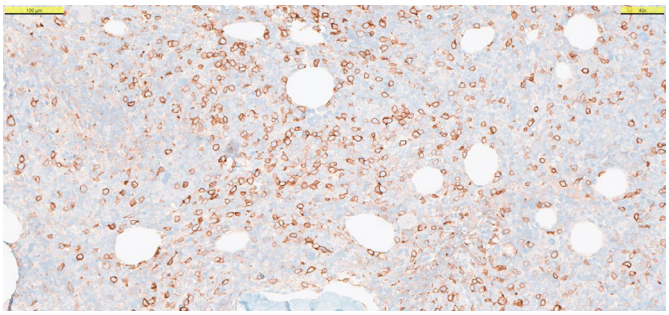

Figure 1. Memranous/stoplasmic CD34 expression in a myelodysplastic syndrome case (x400)

Although no significant differences were observed among all three groups with respect to CD34 staining intensity (p=0.06), a significant difference was observed in terms of CD34 staining pattern (p=0.01). Nuclear staining or membranous staining alone was not observed in any of the cases. The paired comparisons revealed that particularly the membranous/cytoplasmic staining pattern with CD34 was significantly higher in MDS cases when compared to the other two groups.

A significant difference was observed between MDS, MPN and control groups in terms of CD117 staining rate (p<0.01). In the vast majority (90%) of the control group, a staining rate

less than 5% was observed for CD117, while staining rates equal to 5% and higher were found in 73.3% of the MDS cases and in 82.7% of the MPN cases (**Table 2, Figure 2**).

Table 2. CD117 expression results in MDS, MPN and control groups

CD117 Staining rates	Control group		MDS Group		MPN Group		Total	
<%5	27	%90	8	%26.7	5	%17.2	40	%44.9
%5-30	3	%10	18	%60	24	%82.8	45	%50.6
>%30	0	0	4	%13.3	0	0	4	%4.5
CD117 Staining intensity								
1(+)	11	%36.7	7	%23.3	1	%3.4	19	%21.3
2(+)	14	%46.7	12	%40	15	%51.7	41	%46.1
3(+)	5	%16.7	11	%36.7	13	%44.8	29	%32.6
CD117 Staining pattern								
Cytoplasmic	25	%83.3	26	%86.7	24	%82.8	75	%84.3
Membranous /cytoplasmic	5	%16.6	4	%13.3	5	%17.2	14	%15.7
Total	30	%100	30	%100	29	%100	89	%100

MDS: Myelodysplastic Syndrome, MPN: Myeloproliferative Neoplasm

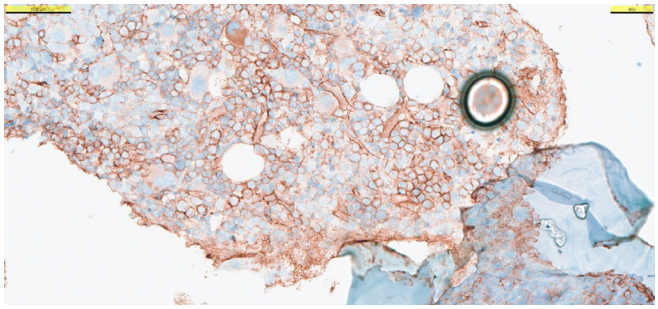

Figure 2. Memranous/stoplasmic CD117 expression in a myeloproliferative neoplasm case (x400)

None of the cases with CD117 staining showed only membranous or nuclear staining. Regarding the CD117 staining pattern, no significant differences were observed between the groups (p=0.90).

When compared to the control group, both MDS and MPN groups had statistically substantially higher frequencies of β-catenin staining (p<0.01) (**Figure 3**).

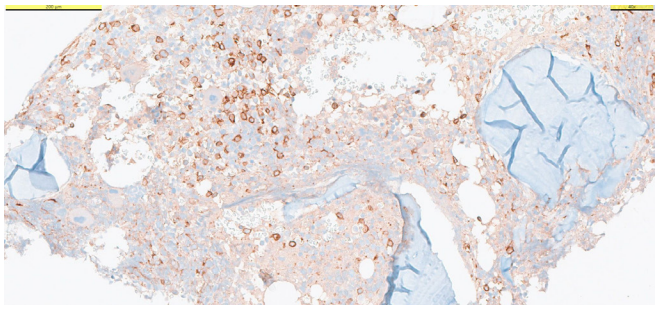

Figure 3. Memranous/stoplasmic β-catenin expression in a group of 'atypical localization of immature precursors' (ALIP) in a myelodysplastic syndrome case (x400)

No significant difference was observed among all three groups in terms of β-catenin staining intensity (p=0.32). Level 1(+) staining with β-catenin was observed in 86.5% of all cases, while level 2(+) staining was found in 13.4% of the cases. Cytoplasmic staining was observed in 96.6% of all cases (**Table 3**).

Table 3. β-catenin expression results in MDS, MPN and control groups.

β-catenin staining rates	Control Group		MDS Group		MPN Group		Total	
<%5	30	%100	10	%33.3	17	%58.6	57	%64
%5-30	0	0	20	%66.6	12	%41.4	32	%36
>%30	0	0	0	0	0	0	0	0
β-catenin staining intensity								
1(+)	24	%80	28	%93.3	25	%86.2	77	%86.5
2(+)	6	%20	2	%6.7	4	%13.7	12	%13.4
3(+)	0	0	0	0	0	0	0	0
B-catenin staining pattern								
Cytoplasmic	29	%96.7	28	%93.3	29	%100	86	%96.6
Membranous /cytoplasmic	1	%3.3	2	%6.6	0	0	3	%3.3
Total	30	%100	30	%100	29	%100	89	%100

MDS: Myelodysplastic Syndrome, MPN: Myeloproliferative Neoplasm

Examining the correlation between the expression rates of all three markers, a potent correlation (0.50-0.75) was observed between CD34 and CD117, as well as CD117 and β-catenin, in both MDS and MPN cases. A weak correlation (0.25-0.50) was observed between CD34 and β-catenin. In the control group, correlations between CD34 and CD117 were weak (0.25-0.50), while correlations between CD34 and β-catenin were minimal (0.25) and correlations between CD117 and β-catenin were strong (0.50-0.75).

DISCUSSION

MPN, first described by Dameshak in 1951, are clonal diseases of pluripotent hematopoietic stem cells characterized by neoplastic proliferation at least in one series in bone marrow. Due to clonal expansion, hematopoietic series exhibit an abnormally high level of proliferation and hematopoiesis. In contrast to acute leukemias, the maturation of cells is complete and the natural course of the disease is chronic in MPN.

MDS is a group of clonal stem cell diseases characterized by ineffective and dysplastic hematopoiesis and has a high risk for progression to acute leukemia. The most significant prognostic indicator for MDS is high blast count in blood and bone marrow.[5] Blast count is essential for the diagnosis and subtyping of numerous clonal hematopoietic diseases.

In a large number of studies, many surface antigens were tested for marking progenitor cells.[16,17] CD34 was one of the most investigated surface antigens that was found to be uniquely expressed on stem cells in studies.[18] It was observed to be significantly elevated, particularly in cases of high-grade MDS, which demonstrates an increased ALIP clusters and count of blast cells. In accordance with this, in this study we observed substantially higher staining in MDS and MPN cases compared to the control group.

Furthermore CD117 was demonstrated to be more dependable and superior than various surface antigens. Although CD117 may be expressed in numerous non-hematopoietic tissues and in all bone marrow cell types, it has demonstrated a high level of specificity for the myeloid cell types in particular. Muroi et al.[19] reported that CD117 is the most trustworthy marker for identifying myeloblasts.In hematological diseases progressing with megakaryocytic and erythroid involvement, the expression of this gene was found to be much lower or even absent.[8] Di Noto et al.[20] identified CD117 positivity in 62% of AML cases, in 64.7% of chronic myeloid leukemia patients with myeloid blast crises and in 92.8% of advanced MDS cases. Nomdede'u et al. and Pirruccello et al.[18-21] discovered CD117 expression in MDS blast cells at a rate of 91.6% and 57.2%, respectively.Similar to the CD34 staining rates, the CD117 staining rates of the cases in our study were substantially distinct from those of the control cases when compared to the MDS and MPN groups. Furthermore the staining frequencies for CD34 and CD117 increase with increasing grade and blast count.

Although there is no statistically significant difference between MPN and MDS in terms of CD34 and CD117 staining rates, MPN cases tend to exhibit CD117 staining rather than CD34 staining. Since CD117 is primarily myeloid-specific, the higher CD117 staining rates observed in MPN cases are to be expected. Due to the prevalence of myeloid proliferation in MPN, the increase in granulocyte/macrophage series progenitors is substantially greater than that of other progenitors.

β-catenin is a cytoplasmic protein that serves as a component of the Wnt signaling pathway. Numerous studies have demonstrated a substantial elevation in the expression of β-catenin in patients of AML22. While β-catenin has been observed in several hematological disorders, its presence in MDS and MPN has only been shown in a limited number of studies.[23] For example, in the study of Jauregui et al., staining rates of more than 5% were observed in 17.3% of 52 MPN cases. In all six of the control cases, there was a staining rate of less than 5%.[24]

In this study, our results indicate that there are notable disparities in staining rates between the MDS and MPN groups when compared to the control group. 66.7% of the MDS cases and 41.4% of the MPN cases exhibited a staining rate of 5% or higher. The tendency of the MDS and MPN cases to exhibit a higher rate of β-catenin staining than the control cases may provide evidence for the role of the proliferation of hematopoietic series and progenitor cells in both diseases and the role of the Wnt signaling system in this proliferation. Consistent with the results of the study in the literature, all control cases had a staining rate of less than 5%. In our study, when considering MPN cases, higher β-catenin staining rates were observed compared to previous researches. The features of the patients as well as technical factors might be to blame for the variation in staining rates between the studies.

No significant differences were observed between all three groups with respect to the intensity of staining for β-catenin. Overall, 86.5% of the cases showed level 1(+) staining while no cases had level 3(+) staining.

In their study, Jauregui et al.[24] observed that β-catenin staining was cytoplasmic in megakaryocytes and perinuclear/ cytoplasmic in erythroid/myeloid series. In some earlier studies, β-catenin was found to be expressed in both cytoplasmic and nuclear localizations in non-hematological neoplasms. In our study we have also observed cytoplasmic staining in 96.6% of the cases. There was no evidence of nuclear staining in any of the cases. Likewise, Subotiki et al.[23] found no nuclear staining of β-catenin in MDS cases in their research. All cases displayed membranous and/or stoplasmic β-catenin staining, and patients with Polistemia Vera had the maximum number of immunexpressing cells.

Jinglan et al.[25] observed nuclear β-catenin staining in myeloblasts and erythroblasts from patients with AML and MDS, noting that nuclear staining indicates that β-catenin is not depleted, is present, and is activated by being transported into the nucleus. They discovered nuclear staining in 40.9% of cases and reported that nuclear β-catenin staining is indicator of poor prognosis in both AML and MDS cases. Nuclear β-catenin staining was observed particularly in cases with high-grade MDS. This study presents a unique investigation of the presence of β-catenin staining in MDS25. The nuclear β-catenin staining is direct evidence for β-catenin activation, which demonstrates the importance of the Wnt/ β-catenin signaling system and that β-catenin activation is directly related to the increase in the number of blast cells in MDS. In our study, in MDS cases, cytoplasmic β-catenin staining was found in erythroid and endothelial cells. The observation of cytoplasmic β-catenin staining in normal erythroblasts suggests that cytoplasmic staining does not necessarily indicate β-catenin activation and that β-catenin exists ordinarily as an adhesion molecule on the inner surface of cell membranes. In support of this data, cases with normal bone marrow, Jinglan et al. also had expression in the cell membranes and cytoplasm.

When evaluating only the MDS cases in our study, CD34 shows superiority to CD117 and β-catenin in terms of staining rate. It is evident that progenitor cells and blasts have a high propensity to stain with CD34. Despite the fact that numerous immune indicators are used to determine an increased blast count, CD34 remains the most reliable marker in this regard. In our study of MPN cases, CD117 staining rates were substantially higher than those of the other two markers. CD117 is a marker which mainly shows a myeloid specificity and is expressed at higher levels in granulocyte/myeloid progenitor cells rather than in primitive hematopoietic progenitors. Therefore, it is expected to stain at high levels in MPN cases, particularly with proliferation in myeloid series. Interestingly, β-catenin staining rates were higher in the control group of our study when compared to the other two groups. β-catenin is an adhesion protein that can also normally be found in the inner cell membrane. It may exist in the cytoplasm even in the absence of any pathology. On the other hand, CD34 and CD117 antigens manifest themselves mainly in the neoplastic proliferation of blasts and progenitor cells.

In our study, we observed a good level of correlation between CD34 and CD117 as well as between CD117 and β-catenin in both MDS and MPN cases, while a weak correlation was found between CD34 and β-catenin. In their study, Ysebaert et al.[26] reported a correlation between β-catenin and CD34 expression. In our study, this correlation was weak.

Limitations of the study

This study had both some quantitative and methodological limitations. The main challenge was studying immunohistochemical techniques without any

antigen loss in long-standing, acid-treated bone marrow blocks. This problem would not exist if the investigation could be conducted prospectively. The assessment of blast staining has the potential to be conducted independently for various subtypes of MDS and MPN. However, this was not undertaken to not to cause the data confusion. Due to the study's single-center design, the potential for a restricted number of instances exists. A potential enhancement to the study would involve conducting a prospective analysis with a larger sample size, which would likely yield more reliable and dependable findings.

CONCLUSION

The overall results of our study show that CD34 is still the most effective marker for the determination of blast count and grade in MDS, while CD117 may have a supportive role in this process and may be particularly useful in the identification of myeloid line progenitors as an ancillary marker. In MPN, CD117 expression is significantly higher than CD34 expression. It is undeniably beneficial, particularly in MPN cases with myeloid proliferation. Specifically, analyzing CD34 and CD117 simultaneously would be an excellent indicator for making the correct diagnosis.

β-catenin, which has subsequently started to be used in hematopoietic diseases, has a high performance in AML cases with the nuclear staining property but cannot show the same performance in MDS and MPN cases. The very limited number of studies conducted on this subject are unable to fully address the questions on the role of Wnt/β-catenin in diseases like MDS and MPN. Future clarification of the function of β-catenin in the diagnosis and treatment of hematological neoplasms will increase as the number of comprehensive studies on this topic increases.

ETHICAL DECLARATIONS

Ethics Committee Approval: This thesis research was authorized in 2010 by the institution of Dicle University.

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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